Amendments to the Drawings:

Submitted concurrently herewith are replacement drawings to a correct minor typographical error in Figure 2D. Specifically, as suggested by the Examiner, "Fr" is replaced with "Tr" in the figure.

REMARKS

Upon entry of the foregoing amendments, claims 1-19, 22, 23 and 25-53 and 57-135 are pending in this case. Claims 6-13, 28, 29, 32, 49-53 and 57-135 are withdrawn. Claims 20, 21 and 54-56 have been canceled in this response without disclaimer of any subject matter therein.

Claim 1 has been amended to recite that the present methods prepare a plurality of substantially uniform nanoparticles. This language describes the advantageous precision by which the methods yield nano-sized particles having virtually any shape or feature, limited only by the shapes and features of the patterned template or substrate. Claim 1 has also been amended to more clearly describe embodiments of the subject matter that the inventors believe is their invention.

Claim 22 has been amended to reflect that the particles are nano-sized. In accordance with this, claims 20 and 21 are canceled.

All of the above amendments are fully supported throughout the specification. Their entry is respectfully requested.

I. Statement of the Substance of the Personal Interview Conducted December 6, 2011

The Applicants sincerely thank Examiners Jessica Worsham and Robert Wax for their time and participation in the helpful personal interview conducted on December 6, 2011. Participating in the interview were Examiners Worsham and Wax, Inventor Dr. Joseph DeSimone and attorneys Shawn Glidden and Bryan Skelton. The Applicants submit the following Statement of the Substance of the Interview.

During the interview, Dr. DeSimone gave a presentation on the claimed subject matter. Dr. DeSimone discussed how the engineered particles are prepared, their uses and the interest that the presently claimed technology has garnered from industry and philanthropists, such as the Bill & Melinda Gates Foundation. During the presentation, the Examiners asked questions regarding the uniformity of the particle's shapes and sizes, and terms of art such as "scum layer" and "sacrificial layer." Applicants believe that the Examiners' questions were addressed completely.

During the interview, Examiner Wax suggested that the claims recite the term "substantially uniform" to describe the monodisperse particles. The Examiners indicated that such amendments and any arguments for patentability would be fully considered in view of the discussion. Submitted herewith are the amendments and arguments. Favorable consideration is solicited.

II. Objections to the Specification are Overcome

Submitted herewith are amendments to correct minor typographical errors in Figure 2D. Specifically, as suggested by the Examiner, "$\mathbf{F_r}$" is replaced with "$\mathbf{T_r}$" in the figure.

Applicants believe that the objection to the specification with regard to "$\mathbf{T_r}$" in the description of Figure 9C was corrected by the filing of a substitute sheet on June 19, 2006.

This is a *bona fide* attempt to be responsive to the objections. If an objection remains, Applicants will make any further necessary changes.

III. Rejection under 35 USC 112, First Paragraph Must be Withdrawn

The Office Action alleges that the methods are not enabled for every type of liquid known, including water. OA, p. 5. Applicants submit that the claims do not have to be enabled for all conceivable embodiments, particularly those that one of skill would not reasonably pursue, *e.g.*, an attempt to make nanoparticles out of pure water. Notwithstanding this fact, the Office Action has not considered that pure water can be made into particles by simply treating the liquid water by lowering the temperature to the freezing point to form solidified water nanoparticles.

According to the Office Action, the level of skill in this field "is high, requiring advanced education and training." Id. According to the MPEP, the test is "whether a skilled person could determine which embodiments that were conceived, but not yet made, would be inoperative or operative with expenditure of no more effort than is normally required in the art." § 2164.08(b), citing *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577 (Fed. Cir. 1984). Consequently, one of skill does not need to be informed precisely by the claim language which liquids are capable of forming solids. An ordinary person of skill in this field, possessing what the Office Action refers to as advanced education and training, would be keenly aware of this information since at the time of filing of the present application, properties of liquids were either known or published, or can be determined routinely.

Applicants respectfully point out that each of the present claims for preparing a particle recite the steps necessary for one of skill in this field to prepare substantially uniform particles. The presently claimed methods are elegant but straight-forward. Therefore, given the present specification's teachings, it is not undue experimentation for one of skill in this field, knowing what she knows, to perform the "treating" step on a liquid that she believes is capable of forming the desired particles.

The Office Action states that "narrowing down the scope to those actually used in the examples lessens the unpredictability of the method." OA, p. 5. Applicants respectfully submit that it is a tenet of patent law that enablement does not require reduction to practice of every embodiment. Finally, requiring such a narrow scope does not provide *quid pro quo* for the Applicants' contribution to this field. Accordingly, Applicants respectfully submit that this rejection must be withdrawn.

IV. Rejections under 35 USC 112, Second Paragraph are Overcome

Applicants believe that most, if not all, of the rejections under § 112, second paragraph were addressed during the interview. The rejected terms are terms of art of which one of skill in this field is aware. To be fully responsive to the Office Action, Applicants are providing the comments below:

a. "affinity for the particles" describes the ability of a substrate to remove particles from the mold. It is a relative term wherein the substrate has a greater affinity for the particles than the particles have for the mold;
b. "essentially free of a scum layer" describes the essential absence of undesirable material that adheres to the patterned template or substrate in the areas between the recesses where the particles reside;
c. "end capping group" is a term of art in this field. It describes the chemical moiety residing at the terminus of a polymer chain. Such groups are well-known in the art;
d. "plurality of recessed areas comprises a plurality of cavities" describes the three-dimensional features that are present on the patterned template or substrate. These are the loci where particles are formed;
e. "surface modification step" is a phrase that describes altering the patterned template surface. Accordingly, methods which can alter the surface are described, *e.g.*, plasma treatment, chemical treatment, etc. and are common steps to one of ordinary skill in the art;
f. "chemical treatment" would be interpreted by one of skill in this field in the context of modifying the patterned template surface. Such processes, such as fluorinating surfaces are well-known;

g. "drawing an implement across the layer" describes an embodiment wherein the layer is contacted with an implement, such as a doctor blade or squeegee to remove material from the surface;

h. "wherein the treating of the liquid material comprises a process selected from the group consisting of a thermal process, a photochemical process, and a chemical process" describes the processes that treat the liquid to transform it into a hardened or thickened material that composes the engineered particle. These processes are described in the specification. One of skill in this field would immediately recognize that, for example, temperature, radiation and chemical treatments are techniques readily available and well understood to harden or thicken a liquid.

i. "batch process, semi-batch process, and continuous batch process" describes well-known production processes for conducting manufacturing methods. Embodiments of the presently claimed methods can be performed using these production processes. Each type of process is well known to one of ordinary skill in the art.

V. The Rejections Under 35 U.S.C. § 103(a) Are Overcome

A. Claims 1-3, 14-17 and 39-48

The Office Action states that claims 1-3, 14-17 and 39-48 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford et al. (WO 2004/096892) ("Hansford"). Applicants respectfully traverse.

According to the Office Action, Hansford teaches "various spreading methods such as micro-pillar and micro-well techniques to form geometrically uniform microparticles." OA, p. 11.

Hansford teaches "the systems and methods disclosed basically fall into to [sic] broad categories, namely the 'micro-pillar' technique and the 'micro-well' technique." However, with regard to geometric uniformity, Applicants respectfully point out that Hansford clearly states that geometric uniformity of the particles is limited to lateral sizes, i.e., two-dimensional uniformity. Hansford states: "Optical profilometry can be employed to confirm that these microparticles have the same lateral sizes as the stamp structures for both the micro-pillar method and micro-well methods." Page 12, lines 7-9., (see also, p. 4, lines 34-35, stating, "microparticles that exhibit well-defined lateral geometries." (Emphases added)).

The reason Hansford describes its particle this way is because the center and rim surfaces of the Hansford particles are not geometrically uniform in three dimensions. Rather, the particles are

described as having "typical" shapes: "Optical profilometry can also be used to confirm that microparticles made with the micro-pillar method are typically thicker in the center portion of the particle, while the microparticles made with [sic] micro-well method typically include a thin central portion but have a thicker rim portion." Id. at lines 9-12 (Emphasis added). Consequently, the particles of Hansford cannot be described as geometrically uniform in three dimensions. This is an important distinction because the method of Hansford is limited in several ways, one of which is the variation in overall three-dimensional physical shape and size of the particles produced.

In fact, the microparticles of Hansford do not substantially mimic the size and shape of the recessed areas of the stamp. Hansford discloses that its exemplified microparticles prepared by the micro-well printing method from wells measuring 40 micrometers wide and about 1.4 micrometers deep, "have an average thickness of about 130nm; however, the rims or outer edges of these microparticles may be as thick as about 300nm to 600nm." Page 8, lines 12-14. Consequently, the variation in the particles' geometries from the wells from which they are formed allows for the rims of the particles to be as much as four times the thickness of the center portion. This incredibly large variation evidences the literal disclosure of the Hansford method cannot be said to engineer or control the three dimensions of its particles, but only the lateral dimension. Even further, Hansford's particles are orders of magnitude in mimicking the size of the wells from which they are formed, i.e., a 130 nanometer thick particle resulting from a 1400 nanometer deep well. The result is that particles having such variability cannot be described as substantially mimicking the patterned recessed areas. With regard to the micro-pillar method, the particles are formed from printing the material coated on the top portion of the pillars of the stamp. The recessed areas of the stamp are not involved in particle formation. Therefore, the particles do not mimic those areas at all.

Hansford describes its particle shape as "typically" having thinner or thicker center or rim portions evidencing that the particle shapes vary. Further, there is no evidence that the center or rim surfaces, *i.e.*, the convex or concave surfaces are engineered or that they can even be controlled. These will always be formed arbitrarily as a result of the final printing step. On a nanometer scale, such arbitrary imperfections are significant as the size of the edges are reported to be three to five times the thickness at the center. Accordingly, the method of Hansford suffers from the inability to form precisely engineered three-dimensionally sized and shaped particles. Absent the present specification's teachings, one of skill in this field following Hansford would not arrive at substantially uniform particle sizes that mimic the features of the recessed areas.

In contrast, as discussed and shown during the personal interview with the Examiners, the presently claimed methods provide precise control over all three dimensions of particle shape and uniformity. The present original specification states that the claimed methods provide for the first time "production of isolated, discrete nanostructures of nearly any size and shape. The shapes presented herein were engineered non-arbitrary shapes." Page 97, lines 9-11. The shapes are "limited only by the original master used to generate the mold." Page 94, lines 4-5. In other words, one of skill in this field would understand that the particles mimic the features of the mold. These statements are evidenced by the scanning electron micrographs of the nanoparticles in the original specification and those shown during the interview.

Additionally, in Hansford's micro-pillar technique, the top of the pillars receives an amount of polymer each time the stamp is coated or filled. As a result, at least one separate printing step is required to remove the layer of polymer from the top of the pillar. This layer is known, in the art, as the "scum layer", which Hansford clearly shows in Figures 2 and 4, and the detailed process descriptions on page 7, step (ii), page 10, step (ii) and page 11, step (vii). Before any microparticle can be prepared from the micro-wells, there must be a separate printing step for each polymer used to remove the "scum layer." In contrast, as discussed during the personal interview and claimed in the present invention, the presently claimed methods do not require a separate step to prepare particles that are essentially free of a scum layer. In fact, the USPTO designated Hansford as failing to teach a method that does not require the additional step of removing the "scum" layer. See Hansford US10/656,661, Final Office Action, dated 10/17/2006, Page 5, para. 2.

In view thereof, Applicants submit that the presently claimed methods are patentable over Hansford.

B. Claims 1 and 4

The Office Action states that claims 1 and 4 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford in view of Rothschild *et al.* (J. Fluorine Chem., 122 (2003), pp.3-10) ("Rothschild"). Applicants respectfully traverse.

According to the Office Action, Rothschild is cited for its teaching regarding the use of PFPE in lithography. As the Action points out, Rothschild states: "It is a key enabler of liquid immersion lithography." OA, p. 13.

In the present claims, the patterned template forms the recesses where the particle will be prepared from a liquid material. For clarity, the "liquid material" recited in the present claims is the material that is disposed on the template and it is from this liquid material that the nanoparticle is

formed. On the other hand, the template that is employed is not a liquid. Though the template may be prepared from a liquid precursor, if it remained a liquid, it could not form recesses in which the particle material could be positioned and it could not perform its function.

Rothschild, in contrast, is discussing immersion lithography, which is a different process that requires a liquid throughout the process. Rothschild states: "In this scheme a transparent liquid is introduced between the last optical element and the photoresist-coated wafer, enabling an effective NA of ~1.3." Page 9, under the heading "Immersion Lithography with fluorine-based liquids." Rothschild actually states: "The key enabler of liquid immersion lithography at 157 nm is a liquid...." Id. (Emphasis added). In summary, Rothschild is using an entirely distinct liquid immersion lithographic process that requires the PFPE liquid to remain a liquid. Accordingly, it cannot be properly said that Rothschild is a teaching that PFPE is enabling any method other than the liquid-based lithography method of Rothschild.

The teachings and deficiencies of Hansford are discussed above. The combination of Rothschild merely adds the teaching of PFPE that must be a liquid throughout its entire use in a completely different process. Accordingly, Rothschild does not remedy the deficiencies of Hansford.

C. Claim 5

The Office Action states that claim 5 has been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford in view of Rothschild in further view of Meijs et al. (WO 96/31548) ("Meijs"). Applicants respectfully traverse.

According to the Office Action, Meijs teaches a perfluoropolyether of formula 1 that is not taught in either Hansford or Rothschild. OA, p. 13. The Office Action states that, "using the perfluoropolyether described in formula 1 would also enable photolithography because it falls within the class of perfluoropolyethers." OA at p. 14.

Applicants respectfully point out that using the perfluoropolyether described in Meijs would render Rothschild and Hansford inoperable.

The polymers of Meijs are gel-like solids. Indeed, they are mainly used as corneal transplants. Since the immersion lithography process of Rothschild requires a liquid PFPE, it is not amenable to using the solid polymer of Meijs. Thus, if one were to modify Rothschild in such a way, it would change the principal of operation of Rothschild, and vice-versa. According to the MPEP, if the modification changes the principal operation of the art, the teachings of the references are not sufficient to render the claims *prima facie* obvious. MPEP § 2143.01(VI), Eighth ed., rev.

July 2010, citing *In re Ratti*, 270 F.2d 810 (CCPA 1959). There is also no evidence that the modified Rothschild process would even be operable. "[A] reference teaches away from a combination when using it in that combination would produce an inoperative result." *In re ICON Health & Fitness, Inc.*, 496 F.3d 1374, 1382 (Fed. Cir. 2007); see also, MPEP § 2143.01(V).

Additionally, Meijs teaches that its polymers are prepared "with a porosity sufficient to allow passage therethrough of tissue fluid components...." Page 14, second paragraph. The Office Action provides no evidence that such porous materials could work in the method of Hansford. In fact, in the micro-pillar technique of Hansford, one would not have been motivated to use a porous pillar since at least some of the material would seep into the pillar before any printing could occur. This would only increase the variability in uniformity that plagues Hansford. Likewise, at least some material residing in the well portion of the stamp would seep into the stamp and be lost. Even worse, the material would interlock with the stamp. Consequently, one would not be able to retrieve the material. Thus, there would have been no motivation to combine the teachings of Meijs with Hansford.

Finally, the teachings and deficiencies of Hansford and Rothschild are discussed above. Even should one combine Meijs for its teaching of a porous polymer, the deficiencies of the combination of references remain.

For these reasons, a *prima facie* case of obviousness has not been made.

D. Claims 1, 18-23, 30-31 and 33-37

The Office Action states that claims 1, 18-23, 30-31 and 33-37 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford in view of Shastri (US Patent Appl. Pub. No. 2004/0115239) ("Shastri"). Applicants respectfully traverse.

According to the Office Action, "Shastri teaches a layered device having a functional layer comprising particles of a very small size (about 5 nm to about 10 microns), whereby the particles have a predetermined geometric shape...." OA, p. 14. Applicants respectfully point out that the geometric shape described by Shastri does not refer to the shape of its particles.

Shastri teaches that its particles are "substantially spherical." Page 4, para. 0071. This is because the particles are formed as a "colloidal dispersion" whereby the particles are "suspended in an aqueous phase." Page 3, para. 0052 and Page 6, para. 0092. In an aqueous dispersion, like an emulsion or liposomal system, the shape that is generally formed is a spherical shape as a sphere has the lowest surface area to volume ratio which corresponds with the most thermodynamically

stable shape. Accordingly, particles formed from a suspension or emulsion processes will have substantially spherical shapes.

None of the techniques that Shastri describes and references for making particles would be reasonably expected to prepare a plurality of substantially uniform nanoparticles as recited in the presently claimed methods. These techniques are described in Shastri on pages 7 and 8 and are summarized in paragraph 0114. They are essentially: milling, chemical precipitation, condensation and combustion processes. As such, they involve physical or chemical processes that cannot precisely control the physical shape and size of the particles. In fact, Shastri states that the precipitated particles have "varying sizes and shapes." Id. Accordingly, none of the techniques of Shastri are methods that would yield a plurality of substantially uniform nanoparticles.

Moreover, Shastri is directed to delivering its particles by means that are derived from the colloidal dispersion. See, p. 3, para. 0052. "The colloidal dispersion of the present invention is particularly well suited to the targeted delivery of diagnostic and therapeutic agents to specific anatomical structures of a patient by coating or depositing on a surface." Id. Since the particles in the dispersion will be substantially spherical, and the dispersion is "particularly well suited" for Shastri's purpose, there would have been no reason to modify the shape of the particles in its dispersion. In other words, there is no evidence that differently-shaped particles would be of benefit in the dispersion of Shastri.

Regarding the predetermined geometric shapes, Shastri is referring to the shapes of the substrates that are coated with the latex particle dispersions, not the shapes of the particles. The particles themselves, as discussed above, will possess substantially spherical shapes. It follows that using substantially spherical shaped particles to form a layer on a rectangular piece of foil is not the same as forming rectangular-shaped particles. In summary, Shastri's substantially spherical particles do not change their shape when used as a coating.

The Office Action merely concludes that one would combine Hansford with Shastri because "Hansford et al. teach a method of actually forming the polymeric microparticles while Shastri further discuss the characteristics of microparticles formed using a lithography process. ... [I]t would have been obvious that the features found in the products of Shastri could also be formed using the lithography steps of Hansford et al." OA, page 15.

Applicants respectfully point out that this is merely a conclusory statement about the subject matter that may be found in both references. It is not supported by any evidence. Nor does this statement provide any rationale to combine the references. "There must be some articulated

reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR Int'l v. Teleflex Inc.*, 550 U.S. 398, 418 (2007) (quoting *Kahn,* 441 F.3d 977, 988). Accordingly, the Office Action fails to establish a *prima facie* case of obviousness.

E. Claims 1 and 25-27

The Office Action states that claims 1 and 25-27 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford in view of Xia *et al.* (Science, v. 273, pp. 347-349 (1996)). Applicants respectfully traverse.

According to the Office Action, "Xia et al. teach replica molding which is a well-known process in formation of patterned templates…." OA, p. 16.

Applicants respectfully submit that the manner of making the patterned template or the template material itself in Xia would not materially change the method of Hansford. As discussed above, Hansford teaches that its microparticles are prepared by micro-pillar and micro-well techniques. According to Hansford: "Optical profilometry can also be used to confirm that microparticles made with the micro-pillar method are typically thicker in the center portion of the particle, while the microparticles made with [sic] micro-well method typically include a thin central portion but have a thicker rim portion." Id. at lines 9-12 (Emphasis added). Thus, Hansford's micro-pillar and micro-well techniques prepare particles that have typical variations in the three-dimensional size and shape of each particle. Accordingly, the particles do not mimic the shape or size of the wells from which they are formed. Therefore, should one of skill combine the mold of Xia with the Hansford micro-well or micro-pillar technique, she would still not arrive at the presently claimed methods that prepare substantially uniform nanoparticles that substantially mimic the three dimensional size and shape of the recessed areas of the template from which they are formed.

F. Claims 1, 38 and 54-56

The Office Action states that claims 1, 38 and 54-56 have been rejected under 35 U.S.C. § 103(a) as being unpatentable over Hansford in view of Anderson, *et al.* (U.S. 6,645,432). Applicants respectfully traverse.

According to the Office Action, combining Hansford and Anderson would have been obvious "because both teach molding methods using stamps to make products." OA, p. 17.

Without acquiescing to any reasoning in the Office Action for combining the references, Applicants respectfully point out that the Office Action uses the teachings of Anderson merely to

show interconnected structures in the polymeric membrane. However, neither this teaching in Anderson or any other teaching in Anderson remedies the deficiencies in the teachings of Hansford, which are discussed above. For at least this reason, a *prima facie* case of obviousness has not been made.

Additionally, Anderson is directed to a microfluidic device, which is a device formed with channels to flow materials therethrough. A microfluidic device cannot function with channels that do not have an entry port and an exit port for flowing materials since a material will not flow through a channel that does not have two openings.

In direct contrast, Hansford's micro wells are dead-ended.

The Office Action alleges that it would have been obvious to combine Anderson and Hansford because both teach molding methods to make products. OA, page 17. Applicants respectfully point out that this is merely a conclusory statement about the subject matter that may be found in both references. This statement does not provide any rationale to combine the references. "There must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *KSR* (2007). Indeed, the products of Anderson are microfluidic devices as described above. These products have no applicability to the products produced in Hansford. Accordingly, for this additional reason, the Office Action fails to establish a *prima facie* case of obviousness.

CONCLUSION

In view of the above amendments and remarks, claims 1-5, 14-19, 22, 23, 25-27, 30-31 and 33-48 are patentable. A notice to this effect is respectfully requested.

If there are any issues remaining which impede allowance of any of the pending claims, Applicants request the Examiner call the undersigned attorney to discuss so that the prosecution of this application can move forward.

It is not believed that extensions of time or fees for net addition of claims are required, beyond those, which may otherwise be provided for in documents accompanying this paper. However, in the event that additional extensions of time are necessary to allow consideration of this paper, such extensions are hereby petitioned under 37 CFR § 1.136(a), and any fee required

therefore (including fees for net addition of claims) is hereby authorized to be charged to Deposit Account No. 16-0605.

Respectfully submitted,

/bryan l. skelton/

Bryan L. Skelton
Registration No. 50,893

CUSTOMER NO. 00826
ALSTON & BIRD LLP
Bank of America Plaza
101 South Tryon Street, Suite 4000
Charlotte, NC 28280-4000
Tel Research Triangle Area Office (919) 862-2200
Fax Research Triangle Area Office (919) 862-2260
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